filtered. The spent catalyst was boiled in benzene and the benzene solution added to the filtrate. After evaporation of the solvent the residue was crystallized from benzene. The yield was 52 mg. (0.8%), m.p. 203–204°.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.47; H, 5.67. Found: C, 84.12; H, 5.76.

8,8'-Diphenyl-2,2'-biquinoline. The method of preparation was similar to that used for 8,8'-dimethyl-2,2'-biquinoline. From 6 g. of 8-phenyl-2-bromoquinoline, 71 mg. (1.7%) of purified product was obtained. After crystallization from benzene it melted at 247–248°.

Anal. Calcd. for $C_{30}H_{20}N_2$: C, 88.21; H, 4.94. Found: C, 88.37; H, 4.94.

8,8'-Diethyl-2,2'-biquinoline. A mixture of 7.5 g. of 8-ethyl-2-bromoquinoline and 10 g. of copper powder pretreated by the method of Kleider and Adams[18] was heated for 3 hr. at 210–220°. The reaction mixture was pulverized and extracted with hot concentrated hydrochloric acid. The acid extracts were cautiously neutralized with aqueous sodium hydroxide and then made strongly alkaline with ammonium hydroxide. The mixture was extracted with benzene and the extracts were concentrated to a small volume. The solution was adsorbed on an alumina column. Hexane and hexane-chloroform mixtures were used as eluents with fractions taken at every 20 ml. The residue from evaporation of the solvents was crystallized from benzene yielding 0.156 g. (3.1%) melting at 122–123°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45. Found: C, 84.51; H, 6.41.

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5-Bromoörotic Acid

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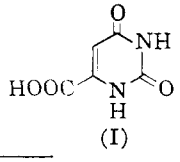
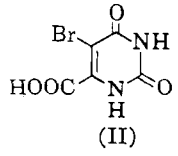
In the past few years, increased interest in the physiological properties of orotic acid (I) and its derivatives has been apparent. A variety of 5-substituted orotic acids have been investigated, including 5-halogenated derivatives; 5-chloroörotic acid was described by Johnson[1] in 1943, 5-iodoorotic acid has been synthesized and used to elucidate aspects of nucleic acid metabolism,[2] and the effect of 5-fluoroörotic acid on tumor growth has recently been studied.[3] However, no reliable synthesis or description of 5-bromoörotic acid (II) has been available.



(I)



(II)

Several reported attempts to brominate orotic acid directly in aqueous solution resulted in the formation of 5,5-dibromobarbituric acid.[4,5] Behrend[6] suggested that oxidation of 5-bromo-6-methyluracil with hot, fuming nitric acid gave 5-bromoörotic acid, but the yield was very poor and the product was not clearly described.

Although uracil[7] and 6-methyluracil[8] have been brominated in the 5-position in high yield by reaction with bromine in carbon disulfide, we recovered only unchanged starting material when orotic acid was treated with bromine in carbon tetrachloride at 70°. However, reaction with a mixture of aqueous hydrogen peroxide and hydrobromic acid led to a 73% yield of bromoörotic acid. The dihydrate crystallized from aqueous solution, and was converted to the anhydrous compound by heating at 80° *in vacuo* over phosphorus pentoxide. It was recovered unchanged after being boiled with aqueous sodium hydroxide solution, which indicates the stability of the C—Br bond and proves it to be at the 5-position as expected.

Potentiometric titration showed 5-bromoörotic acid to be dibasic, the $-\log$ of the apparent acidic ionization constants being 2.21 and 7.59. The corresponding values for orotic acid itself are 2.40[5,9] (2.8[10,11]) and 9.45,[10,11] while the value for o-bromobenzoic acid is 2.85.[9,12]

Upon heating above its melting point, the acid was smoothly decarboxylated to give a nearly quantitative yield of 5-bromouracil. Conversely, orotic acid itself has only recently been decarboxylated successfully, under drastic conditions, and the yield of the resulting uracil was low.[13]

EXPERIMENTAL[14]

Attempted direct bromination of orotic acid. Orotic acid monohydrate (25.0 g., 0.144 mole) was slurried with 100 ml. dry carbon tetrachloride, and bromine (23 g., 0.144 mole) was added dropwise with stirring. The red mixture was then boiled under reflux for several hours, cooled, and the solid filtered off and washed with carbon tetrachloride. After drying in air, the residue was recrystallized from water to give a quantitative recovery of orotic acid, m.p. 342° (decomp.) (immersed at 340°).

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Anal. Calcd. for $C_5H_4N_2O_4 \cdot H_2O$: C, 34.5; H, 3.47; N, 16.1. Found: C, 34.7; H, 3.54; N, 16.2.

5-Bromoörotic acid. Orotic acid monohydrate (52 g., 0.30 mole) was suspended in 30% aqueous hydrogen peroxide ("Superoxol") (63 ml., 0.80 mole) at about 0°, and 90 ml. (0.80 mole) 48% aqueous hydrobromic acid was added dropwise with mechanical stirring. The violent reaction was moderated by ice cooling to maintain the temperature below 35°. After addition of the hydrobromic acid was complete, the mixture was allowed to stand overnight. The precipitated solid was isolated by filtration, washed with cold water, and dried to give a 73% yield of crude product.

Recrystallization from water gave pale yellow needles of 5-bromoörotic acid dihydrate, m.p. 288° (dec.) (immersed at 280°).

Anal. Calcd. for $C_5H_3BrN_2O_4 \cdot 2H_2O$: C, 22.2; H, 2.60; N, 10.3. Found: C, 22.8; H, 2.57; N, 10.3.

The anhydrous acid was obtained by drying at 80° over phosphorus pentoxide.

Anal. Calcd. for $C_5H_3BrN_2O_4$: C, 25.6; H, 1.29; N, 11.9. Found: C, 25.6; H, 1.27; N, 12.1.

A sample of 5-bromoörotic acid was boiled for 1 hr. with 10% aqueous sodium hydroxide solution, and was recovered unchanged after acidification, isolation, and drying. Samples of the acid were titrated in approximately 0.01*M* aqueous solution with 0.100*M* sodium hydroxide solution. A Photovolt *p*H meter, equipped with standard glass and calomel electrodes, was employed for these measurements, and the usual precautions were observed. The *p*H of the solutions at 50% of the stoichiometric volume of alkali was taken as pK_a' for each ionizing group. The pK_a' calculated from eight other points on the titration curves was in reasonable agreement with these values. 5-Bromoörotic acid was found to have pK_{a1}' of 2.2_1 and a pK_{a2}' of 7.5_9.

The ultraviolet absorption spectrum of a $10^{-4}M$ solution of 5-bromoörotic acid in deionized water was measured with a Beckman Model DU spectrophotometer. At *p*H 5.6, λ_{max} 279.5 mμ ($\epsilon = 8.75 \times 10^3$), λ_{min} 243 mμ ($\epsilon = 1.02 \times 10^3$) were observed.

5-Bromouracil. A 2.0-g. sample of pure 5-bromoörotic acid was carefully heated to about 300° in a Wood's metal bath until gas evolution ceased. The cooled residue was recrystallized from water to give an almost quantitative yield of 5-bromouracil, m.p. 296° (dec.) (lit. 293°).[7]

Anal. Calcd. for $C_4H_3BrN_2O_2$: C, 25.2; H, 1.58. Found: C, 25.3; H, 1.64.

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Improved Syntheses of Certain Derivatives of 5,6-Dimethoxy-8-aminoquinoline[1]

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5,6-Dimethoxy-8-(4′-isopropylamino-1′-methylbutylamino)quinoline (SN-9972)[2] [5,6-dimethoxy-8-butylamino(1′-methyl-4′-diethylamino)quinoline and 5,6-dimethoxy-8-(4′-diethylamino-1′-methylbutylamino)quinoline (SN-8233)[2] have recently provided encouraging data when examined against experimental tumors in animals.[3] It therefore became of interest to develop more efficient syntheses than those heretofore available for these substances.

In the preparation of SN-8233 previously reported[4] the key step involves alkylation of 5,6-dimethoxy-8-aminoquinoline with 1-diethylamino-4-bromopentane (as the hydrobromide) at *p*H 4.8.[5] However, even under the optimum conditions the yield of SN-8233, isolated as the oxalate, was only 21% largely because of cyclization of the bromoamine to 1,1-diethyl-2-methylpyrrolidinium bromide.

Shiho[6] has described the condensation of 1-diethylamino-4-ethoxy-3-pentene with 6-methoxy-8-aminoquinoline followed by reduction of the resulting anil to yield pamaquin. Barber and co-workers[7] have successfully condensed the aminoquinoline with 1-diethylamino-4,4-diethoxypentane to yield the same anil which was similarly reduced to pamaquin in high yield. This general method has been adapted, with some modifications, to the preparation of SN-8233 after attempts to effect the direct reductive alkylation of 5,6-dimethoxy-8-aminoquinoline or 5,6-dimethoxy-8-nitroquinoline with 1-diethylamino-4-pentanone as reported by Bergmann[8] failed. It should also be noted that Barber and co-workers[7] were also unable to obtain pamaquin by Bergmann's method.

In the preparation of the requisite intermediates, unexpected complications were encountered in the bromination of 6-methoxy-8-nitroquinoline. When the method described in detail by Elderfield and co-workers,[9] based on a Japanese report,[10] was followed, the expected 5-bromo-6-methoxy-8-nitroquinoline was not obtained. Rather, what appeared to be a perbromide of the desired compound was isolated. This could be readily converted to the 5-bromo compound by treatment with cyclohexene

(1) This work was supported by a Research Grant (CY-2961) from the National Cancer Institute to the University of Michigan.

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